

Tri-Stable switch

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1 System Description

Tri-stable switch has three devices, each device produces three proteins, two repressor proteins and a reporter protein. The promoter of each device get repressed by proteins produced by other two devices.

2 Assumptions

In ode model of switch, following assumptions have been made:

1. Promoter strength parameters give us the relative amount of produced proteins
2. Minimum repressor protein gives us the minimum amount of protein required to repress the promoter completely
3. Promoter repression is proportional to the amount of corresponding repressor protein present in the cell

3 Model

Boolean Model

We used 'BooleSim'(<http://rumo.biologie.hu-berlin.de/boolesim/>) to understand the limit cycle and attractors. We provided following as the rules:

$A = \text{NOT}(B \text{ OR } C)$

$B = \text{NOT}(C \text{ OR } A)$

$C = \text{NOT}(A \text{ OR } B)$

where, A, B and C are three modules of the switch.

Every switch has been considered as state 1 or 0. Inducers are included in the model as they can change the initial state of each device A, B and C.

ODE model

In ODE modelling, we have taken a simplified approach. In continuation with assumptions listed above, we have used

$$\frac{dA}{dt} = \frac{S_A}{1 + \frac{B+C}{\min(A)}} - \lambda_A * A,$$

where A is the device, B and C are the amount of repressor protein corresponding to promoter of A produced by devices B and C, S_A is the strength of promoter A, λ_A is the degradation rate of protein A,

4 Results

In Boolean model of tri-stable switch, we have a total of 8 possible states. Attractors are states 110, 101, 011, 111, 000, which lead to a limit cycle between states 111 to 000 to 111. While other states 100, 010, 001 don't change their original states. ODE model results are following:

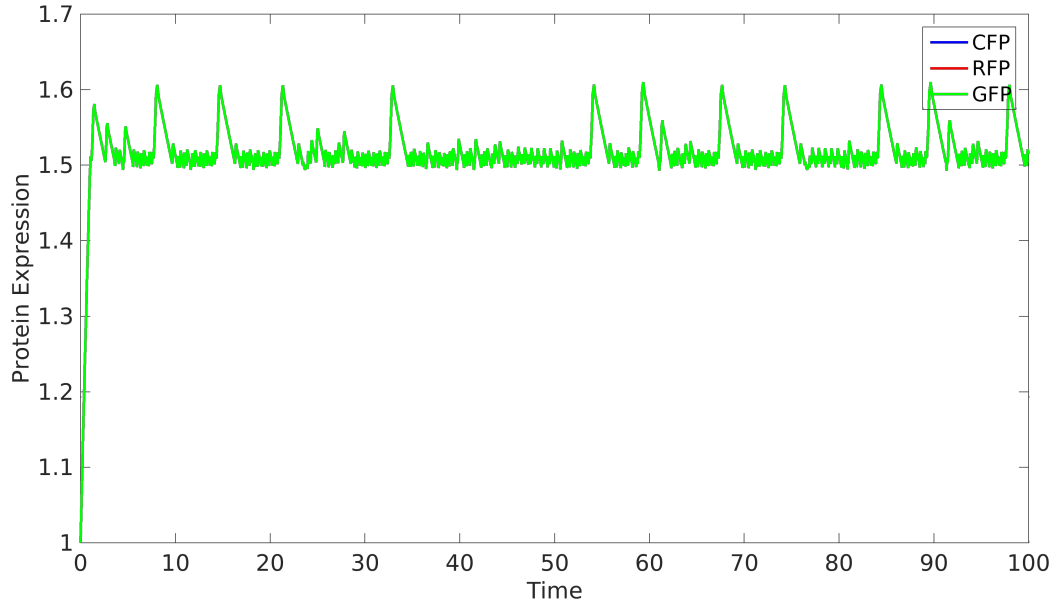


Figure 1: Protein expression with promoter strengths for $A=B=C=1$ with $\min(A)=\min(B)=\min(C)=3$

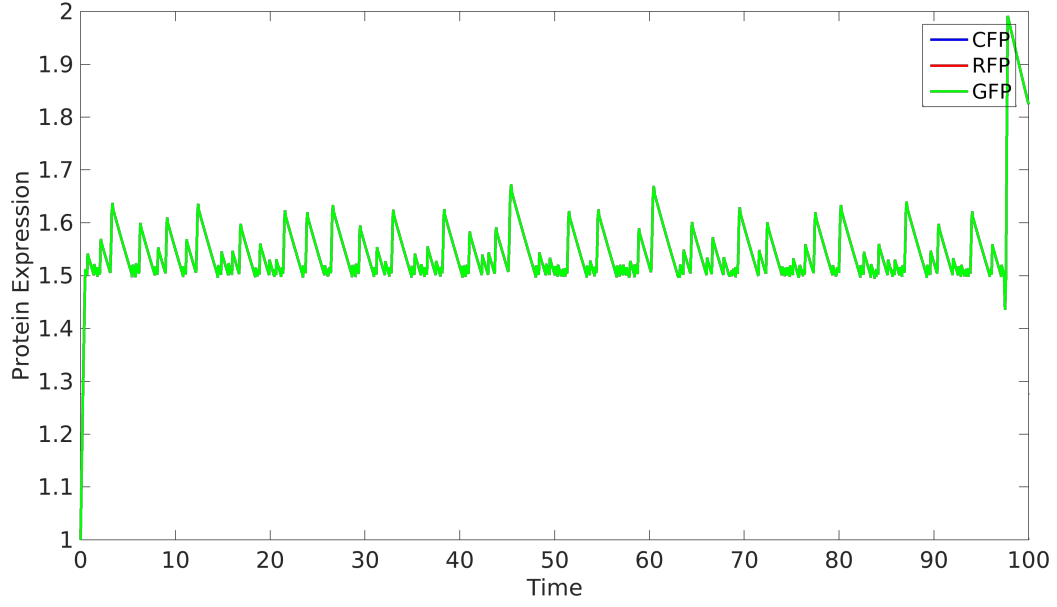


Figure 2: Protein expression with promoter strengths for $A=B=C=2$ with $\min(A)=\min(B)=\min(C)=3$

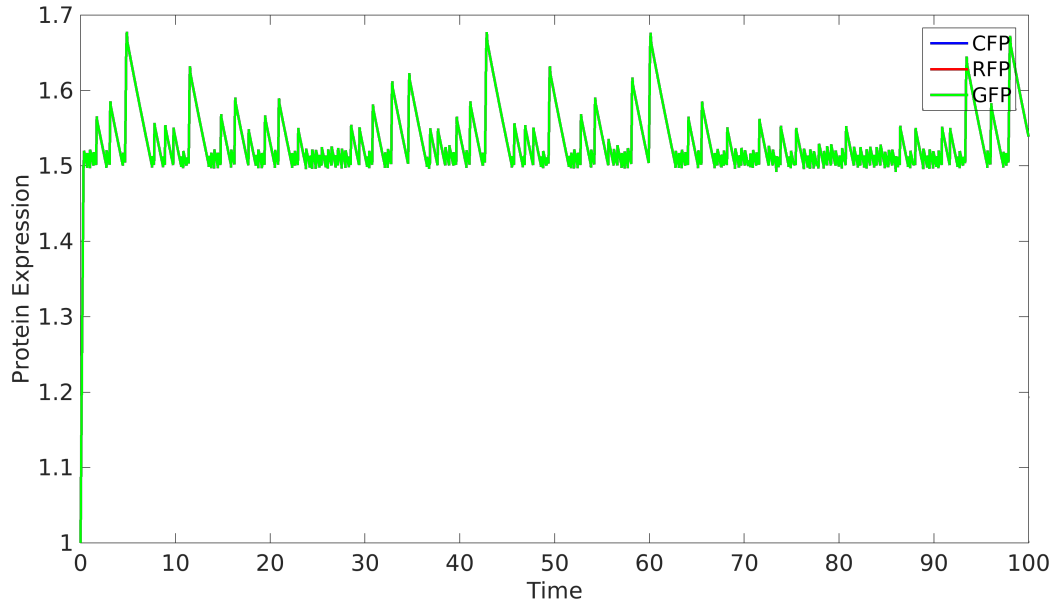


Figure 3: Protein expression with promoter strengths for $A=B=C=3$ with $\min(A)=\min(B)=\min(C)=3$

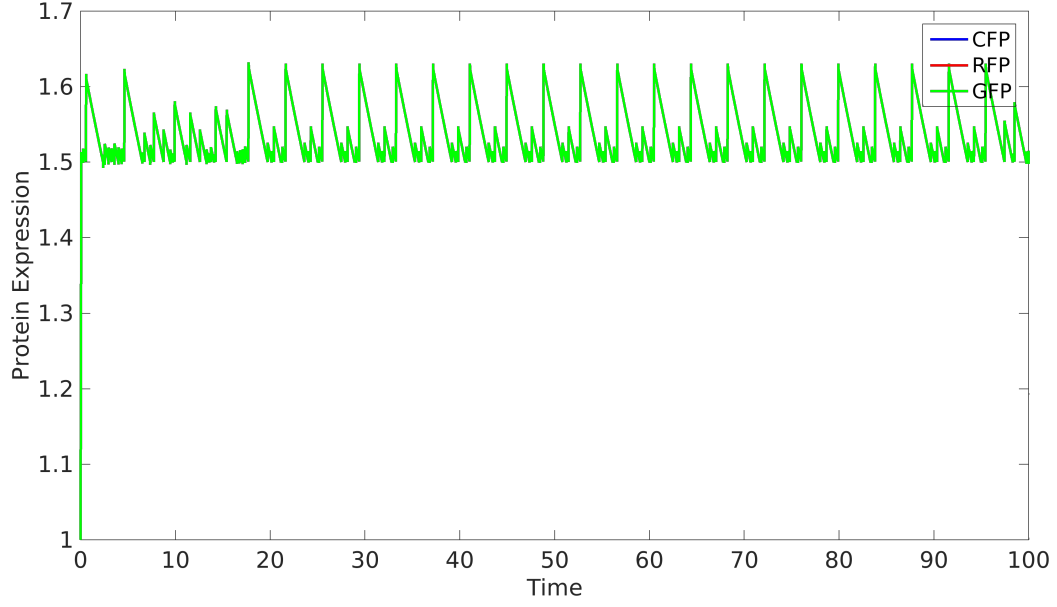


Figure 4: Protein expression with promoter strengths for $A=B=C=12$ with $\min(A)=\min(B)=\min(C)=3$

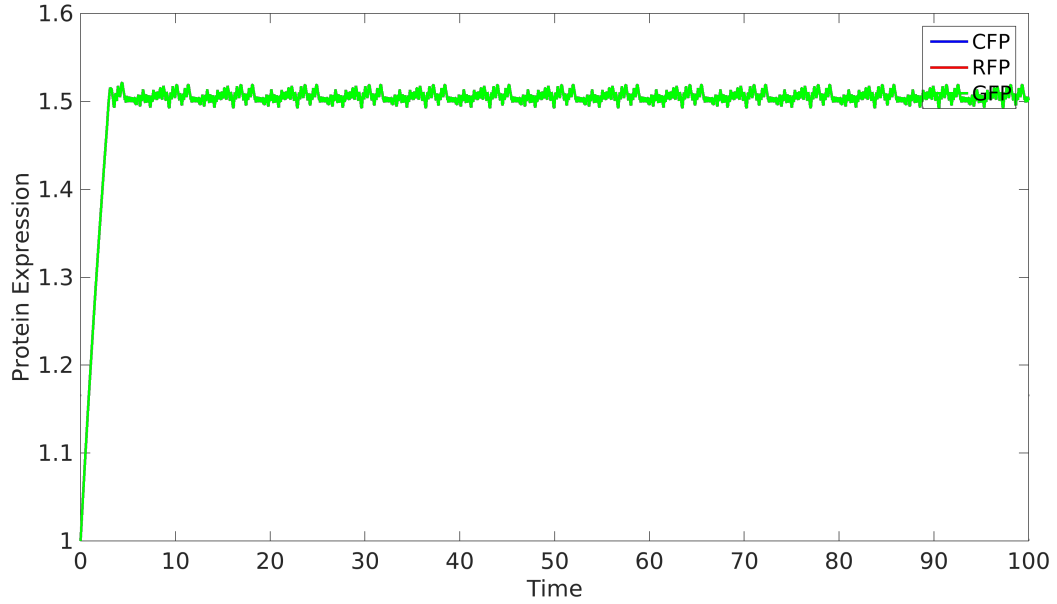


Figure 5: Protein expression with promoter strengths for $A=B=C=0.4$ with $\min(A)=\min(B)=\min(C)=3$

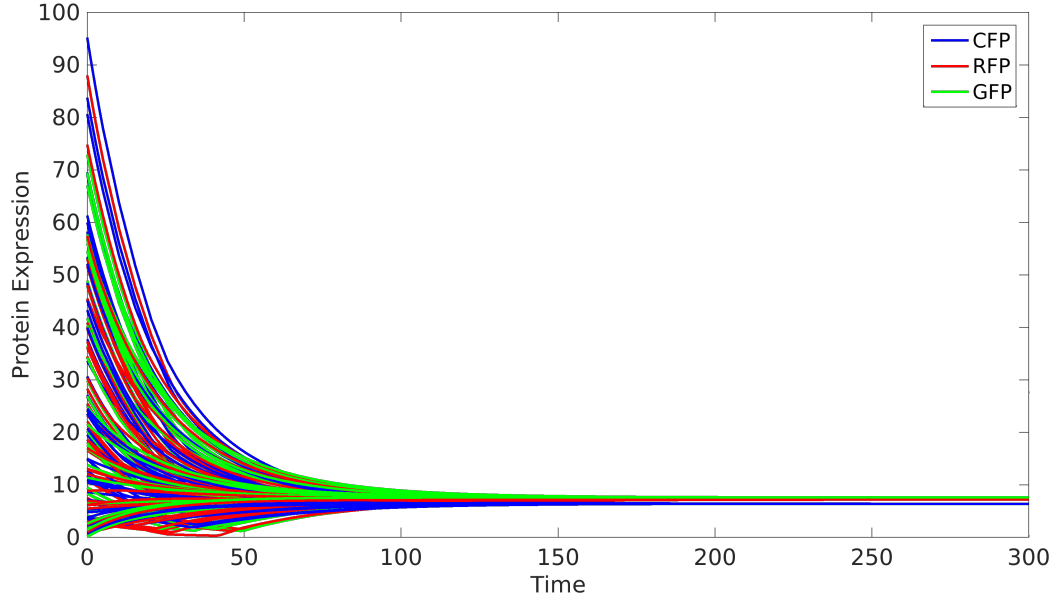


Figure 6: Protein expression with promoter strengths for $A=0.38, B=0.42, C=0.44$ with $\min(A)=\min(B)=\min(C)=30$ for different initial protein concentrations

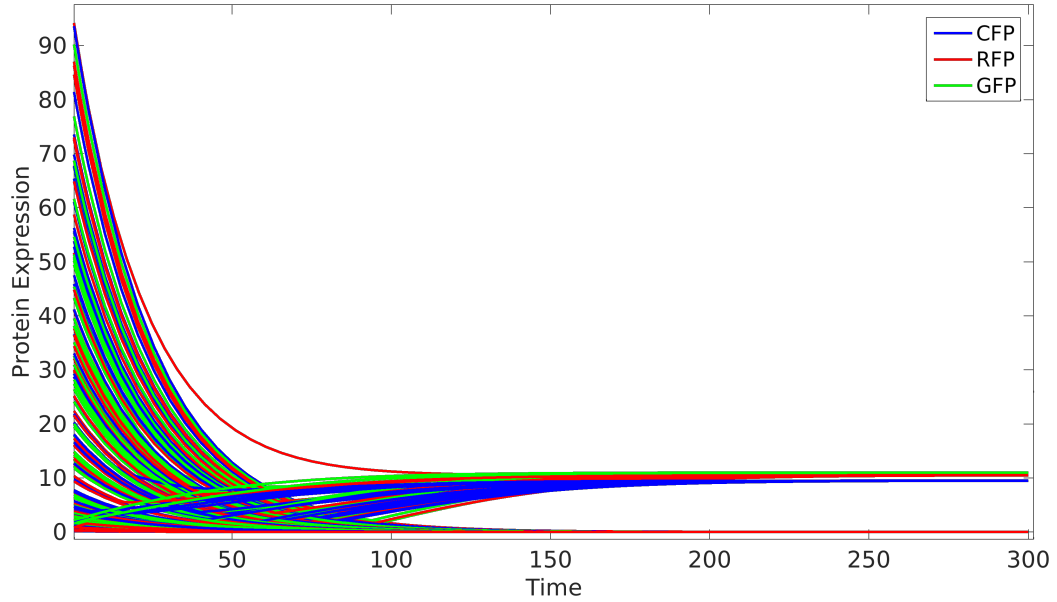


Figure 7: Protein expression with promoter strengths for $A=0.38, B=0.42, C=0.44$ with $\min(A)=\min(B)=\min(C)=3$ for different initial protein concentrations

5 Conclusions

We analyzed the tri-stable switch model using two methods. Boolean model suggests that a limit cycle exists between states 000 and 111. If the strengths of every module is same and promoter strengths & min_repressor protein amount to repress promoters are similar e.g. strength being 2 and the amount of protein required to repress is 3, we can get different type of oscillations/fluctuations.

In ODE model, starting with various initial protein expression levels, we found that tri-stable switch can have more than one stable expressions, depending on min_repressor needed to repress promoters. Here, we have presented two case, one has low requirement of repressor proteins (min=3) and the other one requires high amount (min=30).

6 Code

```
% New tristable switch equations based on HKUST model
function Y=tristableHKUST()

Y0 = [1;1;1]; % Initial concentrations of proteins 1,2 and 3
[t,Y] = ode45(@coupled,[0,500],Y0);

plot(t,Y1(:,1),'b',t,Y(:,2),'r',t,Y(:,3),'g');
size(Y);
legend('x','y','z')

function dYdt=coupled(t,Y)

% Defining constants
d1 = 1.4;% Strength of switch module 1
d2 = 1.4;% Strength of switch module 2
d3 = 1.5;% Strength of switch module 3

kdeg1 = 0.120; % Degradation of repressor protein 1
kdeg2 = 0.140; % Degradation of repressor protein 2
kdeg3 = 0.130; % Degradation of repressor protein 3

min1=30;%Amount of protein required to repress promoter1 completely
min2=30;%Amount of protein required to repress promoter2 completely
min3=30;%Amount of protein required to repress promoter3 completely

if Y(1)+Y(3)<=min2
eqn2 = d2/((1+(Y(1)+Y(3))/min2)) - kdeg2*Y(2);
else
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    eqn2 = - kdeg2*Y(2);
end
if Y(2)+Y(3)<=min1
eqn1 = d1/((1+(Y(2)+Y(3))/min1)) - kdeg1*Y(1);
else
    eqn1 = - kdeg1*Y(1);
end

if Y(2)+Y(1)<=min3
eqn3 = d3/((1+(Y(2)+Y(1))/min3)) - kdeg3*Y(3);
else
    eqn3 = - kdeg3*Y(3);
end

dYdt = [eqn1;eqn2;eqn3];

```